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ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,058	THREADGILL ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,46-53,60-74,76 and 77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27, 46-53, 60-74, and 76-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 21, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made FINAL.

Claims 1-27, 46-53, and 60-74, and 76-77 are currently pending. Claims 1, 2, 46, 47, 60, 64, and 74 have been amended. Claims 76 and 77 are newly presented. Therefore Claims 1-27, 46-53, and 60-74, and 76-77 will be addressed herein.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-10 and 60 remain rejected under 35 U.S.C. 102(a) as being anticipated by Howard et al (Mammalian Genome March 2000) for the reasons set forth in the Office Action of September 21, 2006.

Regarding Claims 1-10 Howard et al teach a method comprising (a) providing a renewable population of genetically diverse individuals; and (b) mapping the genomes

of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Specifically Howard et al teach that the recombinant inbred lines AXB and BXA (which are both homozygous) were both used to study a mouse mutation that causes altered mammary gland development. Backcross and intercross of the AXB and the BXA lines display both alterations in the number and placement of nipples. Approximately 25% of both the AXB and BXA intercrosses and approximately 50% of the female backcross mice observed the mutant phenotype. Howard et al also teach that they are now mapping the ska gene in the AXB/BXA recombinant inbred strains of mice and in the back cross and intercross panels in order to make a high resolution map to isolate the ska locus.

4. Claims 1-10, 15, 19-27, 46-53, 64-74 (and new claims 76-77) remain rejected under 35 U.S.C. 102(b) as being anticipated by Diehl et al (PNAS 1997) for reasons set forth in the Office Action of September 21, 2006 and reiterated below. It is noted that applicants amendment adding new claims 76-77 necessitated the inclusion of those claims in this rejection.

Diehl et al teach a method for identifying multiple genetic loci for example, *Col2a1, Col1a1* and *Col3a1* (page 5235) that modulate the phenotype of facial clefting in mice. Diehl et al have performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse. AXB and BXA

recombinant inbred (RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt. The reference teaches this study for identifying a genetic locus in the diploid mouse system wherein the inbred lines of the renewable population of genetically diverse individuals comprise less than about 100 strains, in one instance a BXD set of 26 RI lines is used (page 5234). Experiments were also performed using the AXB and BXA RI strains to evaluate both spontaneous and teratogen-induced clefting resulting in both visual and physiological phenotypes. The reference uses the extensive data on teratogen-induced clefting in the AXB and BXA RI lines collected previously with a genome wide collection of marker typings for these RI lines to study the effects of genetic polymorphisms segregating in the renewable population (page 5232, left column). Diehl et al. teach the resulting molecular phenotype of their mouse mutants with clefting phenotypes to include for example, eight collagen genes including an altered expression of one, *Col3a1*, which is normally expressed in the embryonic palate. The reference also teaches the method for identifying multiple genetic loci further comprising identifying two or more genetic loci that modulate the phenotype of clefting as seen on the reference's page 5235 in their explanation that in addition to *Col3a1*, two other genetic factors, *Col1a1* and a cyclic nucleotide phosphodiesterase gene are located on the same chromosome and are thought to together, be possibly relevant to the role of cAMP in the etiology of cleft palate abnormalities (page 5235). Additionally, the reference teaches the implication of the tenascin C gene, an extracellular matrix protein, and several cell-signaling molecules which have been previously implicated in clefting. Diehl et al. further teach the modulation of the clefting

phenotype by a non-genetic factor that is a drug exposure and an interaction between two or more non-genetic factors that are drug exposures. The reference reports the findings of a genome-wide search for susceptibility genes for teratogen-induced clefting in the AXB and BXA set of recombinant inbred mouse strains, as they compare the results and the interaction between phenytoin (which induces cleft lip) and 6-aminonicotitinamide (which indices cleft palate) and the cleft palate phenotype (abstract and page 5231). The reference also teaches the method of a non-genetic factors ability to modulate the clefting phenotype wherein the phenotype is modulated by environmental, non-genetic factors such as a fetus' exposure in utero to ethanol, trimethadione, aminopterin and retinoic acid (page 5231). Included then in these findings are the reference's teachings of the identification of an interaction among two or more non-genetic factors (both environmental and drug-like) and a genetic locus. Furthermore, as stated previously, this same identification was made among multiple genetic loci discovered in this study in addition to those gene mutations that are well known in the art that the present reference reiterates, such as *Msx1*, several *Hox* genes, retinoic acid receptor alpha locus etc, (page 5231). Further Diehl states "Analysis of both human and mouse facial clefting suggest that multiple loci are involved. Our genome wide analyses show that this also appears to be the case for susceptibility to clefting induced by phenytin and 6-AN. While we view our findings as strongly supportive we believe that independent conformation is necessary via studies using both additional RI lines from the AXB and BXA set and backcross and intercross experiments" (See page 5234). Even though Diehl may not have actually backcrossed

or intercrossed the RI lines and used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11-14, 16-18, and 61-63 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Diehl et al. in view of Dindzans et al. (J. of Immunology, 1986) and in further view of Hedrich, Hans J. ("Genetic Monitoring, 1981) for reasons set forth in the Office Action of September 21, 2006 and reiterated below.

The teachings of Diehl et al are presented above.

Diehl et al do not teach the derivation of the RI lines from at least 3, 4 or 8 non-recombinant parent lines or that genetically diverse individuals will be a natural by product from the use of multiple parent strains.

However, Dindzans et al. teach that multiple parents are necessary for the breeding of mice in an attempt to map genes and in the elucidation of mechanisms of genetic control. Dindzans et al. teach "the mode of inheritance of susceptibility/resistance to mouse hepatitis strain 3 (MHV)-3 being determined by typing

the set of AXB/BXA recombinant inbred (RI) strain derived from **resistant** A/J and **susceptible** C57BL/6J progenitors for susceptibility to infection as determined by the severity of live pathology". "The strain distribution pattern for susceptibility showed a discontinuous variation: one strain was fully resistant (like A/J), four strains were fully susceptible (like C57BL/6J), and 16 strains showed an intermediate degree of susceptibility"(page 2355). Accordingly, it has been suggested that strain-dependent susceptibility to MHV-3 reflects genetically controlled immune defects rather than differences in the non-genetic, in this case viral factor. It is important to note the need for parental strain diversity that the reference teaches as " the AXB/BXA RI strains used in these experiments were derived from susceptible (C57BL/6J) and resistant (A/J) progenitors representing extremes in disease" for the sole purpose of creating RI strains exhibiting distinct patterns of MHV-3 induced liver pathology, and a discontinuous strain distribution pattern of S/R was seen (page 2357, discussion). This reference then teaches the importance of having a "unique assortment of parental genes that are homozygous at every locus, as such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control"(page 2355). The reference teaches that multiple progenitors were used to establish their population for the expected benefit that using multiple progenitors creates a "unique assortment of parental genes" which is "useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control".

Dindzans et al. do not teach the derivation of the RI lines from at least 3, 4 or 8 non-recombinant parent lines.

Hedrich teaches the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. Hedrich teaches in his Chapter on "genetic monitoring" of the mouse in biomedical research, that the organization of breeding colonies should include propagation steps consisting of three groups: "foundation colony (FC), pedigreed expansion colony (PEC), and production colonies (PC)"(Chapter 8, Page 171). Hedrich further teaches that the "foundation colony, which preserves the germline, should be of limited size" and that it may be either be built up as a single line (SL) or in a modified parallel line (MPL) system. With the SL system, Hedrich teaches that "SL colony members are usually more closely related to each other". In contrast, Hedrich teaches that "in the MPL system e.g. three family lines are kept for four generations, each consisting of not more than 8-10 breeding pairs"(Pg. 171). The reference continues to teach that "one breeding pair of the foundation colony is selected as common ancestor, whose offspring will again give rise to three family lines" and further that, "the degree of kinship is varying from generation to generation within the cycle". The reference teaches that this method makes "it possible to select among the lines that one which matches the original standards best".

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl et al. so as to have included the diverse population of non-recombinant, parent lines of Dindzans et al. and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents

would obviously result in a more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best"(Page 171). Therefore, combining the teachings of Diehl et al. in view of Dindzans et al. and in further view of Hedrich would have been obvious at the time the invention was made.

Response To Arguments

7. In the response filed March 21, 2007, Applicants described the presently claimed subject matter as a mapping method wherein a renewable population of genetically diverse individuals is generated and the genomes of this renewable population are mapped in order to identify genetic loci that modulate phenotypes of interest. The Applicants further explained that a "genetically diverse" individual was an individual that was heterozygous for at least one detectable polymorphism. Thus, "genetically diverse" refers to an individual that is not homozygous at every locus (i.e., has different alleles at one or more loci). The Applicants also described a "renewable population" as a population that can be faithfully regenerated. More particularly, it was stated that what must be faithfully regenerated in order to render a population "renewable" are the genomes of the individuals in the population. Thus, natural human populations are not renewable because, for example, if person A and person B were to have a child C, they would not be able to subsequently conceive any other child that was genetically identical to child C because meiotic recombination randomizes the assortment of genes

passed on from each parent to each progeny individual. Simply stated, matings of natural populations (i.e., not inbred populations) cannot produce renewable populations (See pages 11-12 of the response filed March 21, 2007). While the examiner appreciates the explanation of the terms "genetically diverse" and "renewable population" it does not appear that the specification supports the definition of the term "renewable population" provided in the Applicants arguments. On page 18 of the specification it states, "the phrase "renewable population of genetically diverse individuals" refers to a population that can be faithfully regenerated and comprises a limited repertoire of possible genotypes, although individuals within the population are genetically diverse". The term "regenerated" in this definition is not limited to reproducing identical genomes. Thus in the instant case any natural population capable of producing offspring would be considered renewable. The natural population would comprise a limited repertoire of possible genotypes that were present in the parental population. It is further noted that page 6 of the specification teaches that "a renewable population of genetically diverse individuals can comprise: (a) individuals produced by intercrossing recombinant inbred lines; (b) individuals produced by backcrossing recombinant inbred lines; (c) a cloned population of genetically diverse individuals; or (d) a panel of cell lines derived from genetically diverse individuals". In view of the "comprising" language it is unclear if the claims which recite "renewable population" are limited only to a,b,c, and d above or if additional populations could also meet this limitation.

With regard to the rejections over Howard et al the Applicants argued that Howard does not teach providing a renewable population of genetically diverse individuals that are heterozygous for a detectable polymorphism as recited in the instant claims. This argument has been fully considered but is not persuasive. Specifically Howard teaches that crosses of AXB and BXA resulted in a total of 115 F1 progeny (that were genetically identical) and that these mice were then backcrossed and intercrossed (to produce an F2 population that was not genetically identical). While the Applicants state that this F2 population could be employed in a mapping technique, this population of F2 mice is not a "renewable population" because the genomes in the F2 generation could not be regenerated (See page 19 of the response filed March 21, 2007). Since there seems to be no clear definition of the phrase "renewable population" in the specification, the phrase is being given the broadest reasonable interpretation. In the instant case a "renewable population" is being interpreted as any natural population that is capable of producing offspring. Further the Applicants argue that Howard appears to only be mapping the AXB/BXA RI lines and since RI lines are not genetically diverse Howard does not anticipate the instant claims. This argument has been fully considered but is not persuasive because Howard teaches "we are now mapping the ska gene in the AXB/BXA recombinant inbred strains of mice and in our backcross and intercross panels" (See page 237). Thus Howard does in fact teach mapping genetically diverse individuals since the F2 populations produced by the backcrossing and intercrossing are not genetically identical. Thus the rejections made over Howard are maintained.

With regard to the rejections over Diehl et al the Applicants argued that Diehl does not teach each and every element of the claims. Applicants first argue that there is no disclosure that the RI lines were intercrossed. The applicants specifically point out that the Office Action of September 21, 2006 states that "AXB and BXA RI lines derived from crosses between A/J and C5 AXB and BXA recombinant inbred (RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan (page 5232) as a renewable population of genetically diverse individuals". The Applicants however disagree and state that Diehl only teaches that the RI lines were "bred and maintained in a colony at the University of Michigan" (See page 5232 of Diehl). The Applicants further state that Diehl does not teach that the RI lines were intercrossed and that the only breeding that are disclosed in this reference are breedings that are used to maintain the RI lines. This argument has been fully considered and the rejection has been modified to clarify that Diehl does not actually perform intercrossing of RI lines. However it is noted that Diehl states that "while we view our findings as strongly supportive we believe that independent conformation is necessary via studies using both additional RI lines from the AXB and BXA set and backcross and intercross experiments" (See page 5234). Even though Diehl may not have actually backcrossed or intercrossed the RI lines and used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention. Thus the rejections over Diehl are maintained.

With regard to the rejections over Diehl in view of Dindzans and in further view of Hedrich the Applicants argued that the combined references do not teach each and every element of the claims, and further that this combination in fact teaches against the subject matter recited in the claims. With regard to Diehl applicants state that only inbred individuals that are homozygous at every locus are disclosed. This argument has been addressed above. Although Diehl may not have actually backcrossed or intercrossed the RI lines and used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention. With regard to Dindzans applicants state that Dindzans does not teach or suggest the use of heterozygous mice and in fact teaches against the use of such mice. The examiner agrees that this statement is true. The Dindzans reference is only being relied upon to teach how the RI lines were derived, therefore Dindzans is not required to teach a genetically diverse population. With regard to Hedrich applicants state that this reference also teaches the creation of mice that are homozygous at every locus. The examiner agrees that this statement is true. The Hedrich reference is only being relied upon to teach how the RI lines were derived, therefore Hedrich is not required to teach a genetically diverse population. Thus the combination of these references teach how to develop RI lines useful for mapping and Diehl further suggests intercrossing and backcrossing the RI lines to confirm which loci are involved in clefting. For these reasons the rejections over Diehl in view of Dindzans and in further view of Hedrich are maintained.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

Diana B Johannsen

DIANA JOHANNSEN
PRIMARY EXAMINER